REMARKS

A. Status of the Claims

Claims 1-29, 31-33, 38-41, and 43-60 were pending in the case at the time of the filing of this Request for Continued Examination (RCE). Claims 30 and 34-37 have been previously canceled without prejudice or disclaimer. Claims 38-60 are newly canceled without prejudice or disclaimer. Claims 1, 18, 31, and 33 have been amended in the Amendment set forth herein. No new claims have been added. Thus, claims 1-29, and 31-33 are currently under consideration.

Support for the amendments to the claims can be found generally throughout the specification, such as in the claims as originally filed and the following sections of the specification:

Claim 1 – page 5, lines 24-28; FIG. 5; FIG. 6; page 43, lines 2-5; page 44, lines 1-8; page 61, line 12 – 31.

Claim 18 – page 45, lines 15-20; page 45, lines 28-30.

Claims 31 and 33 – page 5, lines 23-28.

B. Rejection of Claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 Under 35 U.S.C. §102(a) as Being Anticipated by Clayman, as Evidenced by Oda *et al.* and Flaitz *et al.*, and as Evidenced by RAC Meeting Minutes

Clayman does not anticipate the claims because it fails to expressly or inherently describe each limitation of the claimed invention. See *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). Clayman does not disclose that the premalignancies or cancers being treated include cells infected with papillomavirus, or induction of apoptosis of a papillomavirus-transformed cell in a hyperplastic lesion.

Nor is there inherent anticipation. Inherent anticipation arises when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co.*, 190 F.3d at 1347. (citing *In re King*, 801 F.2d 1324, 11326 (Fed. Cir., 1986); see also *Atlas Powder Co.,* 190 F.3d at 1347-48). The evidence of record, including Oda and Flaitz, establishes that ***not every malignancy or premalignancy of the cervix or oral cavity involves cells that are infected with HPV.*** (emphasis added). Thus, it is ***not necessary*** for a malignancy or premalignancy of the cervix or oral cavity to include cells infected with HPV.

Slide 8, entitled "Special Protocol Testing Summary Pre Treatment," recites "HPV of microdissected lesion. Applicants note as an initial matter that this slide does not clearly establish that HPV-infected lesions were actually treated. It is possible that the presentation presents a proposed protocol, and not one that was actually implemented. Thus, it is possible that a test for HPV of the microdissected lesion was not performed by the investigators in the actual clinical trial. Even if HPV testing was performed, it is possible that all results might have been negative for HPV, with the study including no participants with HPV-infected lesions. Further, even if a microdissection was performed showing HPV positive cells, it is not clear from Clayman whether the subject were excluded from the study. It is possible that such a subject might have been excluded from Clayman's study. Submitted as Exhibit 1 is a copy of a clinical trial protocol from the National Cancer Institute web site (http://www.nci.nih.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=306522&protocolsearchid=462113) entitled "Phase I/II Study of Oral and Intramucosal Ad5CMB-p53 Gene in Patients with Diffuse Premalignant Carcinoma of the Oral Cavity and Oral Pharynx." The protocol chair is Gary L. Clayman. Exhibit 1, page 3. It is indicated that this information was first published 6/23/03 and last modified on 8/20/07. Exhibit 1, page 1.

Based on the title and entry criteria, it appears that this is another version of the Clayman protocol that is the subject of the Clayman reference cited by the Examiner. It is noted that this protocol makes ***no reference*** to an assessment of HPV status in study participants, or whether HPV positive patients were included in the study, or whether HPV positive patients were excluded from the study.

It is well-established that:

> "inherency ... ***may not be established by probabilities or possibilities***. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (emphasis added). One cannot be certain that in the population of individuals of Clayman that at least one individual had a lesion that included papillomavirus-transformed cells. The ***mere possibility*** that such a lesion might include HPV infected cells is ***not sufficient*** to establish inherent anticipation. Such an interpretation of inherent anticipation is not in line with established case law.

In *MEHL/Biophile*, Milgraum contended that all of the claims of MEHL/Biophile's patent directed to a method for removing hair using a laser were anticipated by an instruction manual. *See MEHL/Biophile,*192 F.3d 1362. The claims included the step of "aligning a laser light applicator substantially vertically over a hair follicle opening." *Id.* The manual taught aiming the laser at skin pigmented with tattoo ink. Milgraum contended that the claims were inherently anticipated because an operator of the laser could use the laser according to the manual without necessarily aligning the laser substantially vertically over a hair follicle opening. *Id.* The Court held that "the possibility of such an alignment does not legally suffice to show anticipation" and that "[o]ccasional results are not inherent." *MEHL/Biophile,*192 F.3d at1365.

Similarly, the mere possibility that one of the lesions set forth in Clayman might contain HPV DNA is not sufficient to establish inherent anticipation. As noted in MEHL/Biophile, ***occasional results are not inherent.*** Without an inherent teaching regarding HPV-transformed cells or apoptosis of any such cell, there can be no anticipation.

Similarly, *Perricone v. Medicis Pharmaceutical Corp.* also supports that the claims are not inherently anticipated. 432 F.3d 1368, 77 USPQ2d 1321, 1328 (Fed. Cir. 2005) In *Perricone*, the claims at issue recited application of the fatty acid ester of the invention to "skin sunburn." *Id.* at 1379. The district court held that this claim was anticipated by Pereira, which disclosed "topical application" of the fatty acid ester. *Id.* In rejecting the district court's finding of inherent anticipation, the Federal Circuit noted:

> The district court's inherent anticipation analysis for this claim contains a flaw. The disclosed use of Pereira's lotion, i.e., topical application, does not suggest application of Pereira's lotion to skin sunburn. In other words, the district court's inherency analysis goes astray because it assumes what Pereira neither disclosed nor rendered inherent. Because Pereira does not disclose topical application to skin sunburn, this court reverses the district court's holding that Pereira anticipates claims 1-4 and 9 of the '693 patent.
> *Id.*

Similarly, in the instant case, there is no inherent anticipation by Clayman because Clayman does not disclose treatment of any lesion that includes papillomavirus-transformed cells, or apoptosis of any such cell as a result of p53 treatment.

In view of the above, it is respectfully submitted that Clayman fails to expressly or inherently anticipate the claimed invention. Therefore, it is respectfully requested that the Board reverse the rejection of each of the currently pending claims that has been rejected under 35 U.S.C. §102(b) based on Clayman.

C. Rejection of Claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 Under 35 U.S.C. §102(b) as Being Anticipated by RAC, as Evidenced by Oda *et al.* and Flaitz *et al.*

As is the case with Clayman, RAC does not anticipate the claims because it fails to expressly or inherently describe each limitation of the claimed invention. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d at 631. RAC does not disclose papillomavirus infection in cells in the lesion or apoptosis of any papillomavirus-infected cell.

For the reasons set forth above with regard to Clayman, the discussion of which is incorporated into this section, there is no inherent anticipation. Without an inherent teaching regarding papillomavirus-transformed cells or apoptosis of any papillomavirus-transformed cells, there can be no anticipation.

Therefore, in view of the above, it is respectfully submitted that RAC fails to expressly or inherently anticipate any of the pending claims at issue in this rejection. Therefore, it is respectfully requested that the Board reverse this rejection.

D. Rejection of Claims 1-14, 19-29, 38-50, and 55-60 Under 35 U.S.C. §102(b) as Being Anticipated by Nielsen as evidenced by Oda *et al.* and Flaitz *et al.*

As is the case with Clayman and RAC, Nielsen does not anticipate the claims because it fails to expressly or inherently describe each limitation of the claimed invention. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d at 631. Nielsen does not disclose papilloma virus infection in cells in the lesion or apoptosis of any papillomavirus-infected cell.

For the reasons set forth above with regard to Clayman and RAC, the discussion of which is incorporated into this section, there is no inherent anticipation. Without an inherent teaching regarding papillomavirus-transformed cells or apoptosis of any papillomavirus-transformed cells, there can be no anticipation.

Therefore, in view of the above, it is respectfully submitted that Nielsen fails to expressly or inherently anticipate any of the pending claims at issue in this rejection. Therefore, it is respectfully requested that this rejection should be withdrawn.

E. Rejection of Claims 1-15, 18-29, 33, 38-51, and 54-60 Under 35 U.S.C. 102(b) as Being Anticipated by El-Deiry

El-Deiry does not anticipate the claimed invention because it does not expressly or inherently disclose administration of a polynucleotide encoding a p53 polypeptide to a papillomavirus-transformed cell. The Board of Patent Appeals and Interferences, in its decision (appeal number 2007-2864), reversed the rejection under 35 U.S.C. §102(b) based on El-Deiry , noting that "we thus agree with Appellant that '[o]ne of ordinary skill in the art would understand that if the exemplified p53 molecule was a human p53, then in the context of the present invention, 'all p53 homologues from other species' refers from p53 molecules from species other than human p53. Thus the ordinary artisan would understand that 'p53' as used in the present specification refers to human p53 and p53 molecules from other species." Decision on Appeal, page 16, quoting Reply Br. 9-10). Thus, because El-Deiry fails to teach "p53" as that term is used in Applicants' specification, it fails to anticipate the claims.

F. Rejection of Claims 16, 17, 31, 32, 52, and 53 as Being Unpatentable Under 35 U.S.C. §103(a) Over Either RAC as Evidenced by Oda *et al.* and Flaitz *et al.*, or El-Deiry in View of Zhang *et al.*

Claims 16, 17, 31, 32, 5, and 53 stand rejected under 35 U.S.C. §103(a) as being obvious over RAC meeting minutes in view of Oda and Flaitz, or El-Diery in view of Zhang. Applicants respectfully traverse.

There is no *prima facie* case of obviousness because the cited combination of references does not teach or suggest each limitation of the claimed invention. For the reasons set forth above, RAC fails to teach or suggest topical application of a composition comprising a

polynucleotide encoding p53 to any lesion that includes papillomavirus-transformed cells or induction of apoptosis in any papillomavirus-transformed cell in a hyperplastic lesion. Further, as discussed above, El-Deiry fails to teach or suggest a polynucleotide encoding a p53.

Oda and Flaitz do not remedy the deficiencies of RAC meeting minutes because while Oda and Flaitz make reference to HPV-transformed cells, they do not provide any teaching or suggestion pertaining to gene therapy of papillomavirus-infected cells. Oda is a reference that concerns chromosomal and cell cycle changes in HPV infected cells when grown in culture. It does not pertain to gene therapy. Flaitz is a review article that concerns a discussion of virus infection and malignancies, and not gene therapy.

Further, Appellants note that Gillison, J. Natl. Cancer Inst, 2000, 92(9):709-20 (C39 in the IDS, and discussed in the specification on page 3) found that HPV was detected in only 25% of its samples of head and neck cancers and that these cancers had distinct biological and clinical features, which is substantially lower than the frequency reported in Oda and Flaitz.

Regarding the deficiencies of El-Diery, Zhang fails to provide the missing teaching or suggestion to provide for topical p53 gene therapy of papillomavirus-infected cells because it is only cited as teaching a flavorant. Further, El-Deiry provides no disclosure pertaining to topical application of any p53 polynucleotide to papillomavirus-transformed cells.

Further, there is no *prima facie* case of obviousness because there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). RAC and El Deiry have been cited as describing delivery of liquid comprising an adenoviral vector to the mouth, and Zhang as teaching a flavorant in a pharmaceutical composition. However, the claims at issue are directed

to methods of inducing apoptosis of a papillomavirus-transformed cell in a hyperplastic lesion in a subject. No specific motivation to provide for inducing apoptosis of a papillomavirus-transformed cell in a hyperplastic lesion in a subject lesion using a flavorant-containing composition containing p53 is identified in these references. Applicants note that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Because there is no teaching, suggestion, or motivation to provide for the claimed invention, there can be no *prima facie* case of obviousness. Therefore, it is respectfully requested that this rejection should be withdrawn.

G. Conclusion

It is respectfully submitted, in light of the above, that none of the pending claims are properly rejected. Reversal of the pending grounds for rejection is thus respectfully requested.

Respectfully submitted,

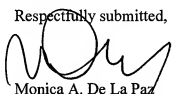

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EXHIBIT 1

National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov

Phase I/II Study of Oral and Intramucosal Ad5CMV-p53 Gene in Patients With Diffuse Premalignant Carcinoma of the Oral Cavity or Oral Pharynx

Last Modified: 8/20/2007 **First Published:** 6/23/2003

Alternate Title

Gene Therapy in Preventing Cancer in Patients With Premalignant Carcinoma of the Oral Cavity or Pharynx

Basic Trial Information

Phase	Type	Status	Age	Sponsor	Protocol IDs
Phase II, Phase I	Prevention	Completed	18 and over	NCI	**MDA-ID-00193** NCI-6053, NCT00064103

Objectives

I. Determine the acute toxic effects of Ad5CMV-p53 gene administered as an oral rinse and as an intramucosal injection in patients with diffuse premalignant carcinoma of the oral cavity or oral pharynx.
II. Determine the maximum tolerated dose of this drug in these patients.
III. Determine the topical transduction efficiency of adenoviral-mediated wild type p53 gene transfer in patients treated with this drug.
IV. Determine the efficacy of this drug in reversing the histology of oral premalignancies in these patients.
V. Determine the distribution of transgenic protein within the area of the premalignant lesion in patients treated with this drug.

Entry Criteria

Disease Characteristics:

- Histologically confirmed mild to moderate dysplasia OR severe dysplasia/carcinoma in situ of the oral cavity or oral pharynx
  - Clinically evident diffuse premalignant disease, defined by 1 of the following mucosal abnormalities:
    - Extension between adjacent organ structures (e.g., lateral tongue, ventral tongue, and the floor of the mouth)
    - Extensive surface area, including the entire ventral tongue or floor of the mouth or buccal mucosa, in a velvety "indiscreet" pattern

- Meets 1 of the following criteria:
  - Previously treated with conventional treatment (e.g., radiotherapy or surgery) for a prior head and neck malignancy
  - Failed biochemoprevention approaches for premalignant disease
  - Failed other therapeutic approaches for premalignant disease

- No active squamous cell carcinoma of the head and neck

Prior/Concurrent Therapy:

Biologic therapy

- See Disease Characteristics

Chemotherapy

- More than 21 days since prior chemotherapy (42 days for mitomycin and nitrosoureas)
- No concurrent systemic chemotherapy

Endocrine therapy

- No concurrent prednisone or the equivalent, including corticosteroids of more than 10 mg/day

Radiotherapy

- See Disease Characteristics
- More than 3 months since prior radiotherapy involving the lesion selected for this study
- No concurrent radiotherapy

Surgery

- See Disease Characteristics

Other

- More than 8 weeks since prior investigational agents
- No prior experimental therapy (i.e., oral, systemic, topical, or direct injection) for the lesion selected for treatment in this study
- No other concurrent immunosuppressive therapy
- No other concurrent investigational agents
- No concurrent aspirin dose greater than 175 mg/day

Patient Characteristics:

Age

- 18 and over

Performance status

- Karnofsky 70-100%

Life expectancy

- Not specified

Hematopoietic

- Absolute granulocyte count at least 2,000/mm^3
- Platelet count at least 100,000/mm^3

Hepatic

- Bilirubin no greater than 1.0 mg/dL

Renal

- Creatinine no greater than 1.5 mg/dL

Cardiovascular

- No hypertension (baseline blood pressure 140/90 mm Hg or higher)

- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective barrier contraception during and for 1 year after study participation
- HIV-1 negative
- No known contact with former tissue or organ transplantation recipients or individuals with severe immunodeficiency disease (acquired or congenital) during and for 28 days after study treatment
- No prior malignancy within the past 2 years except nonmelanoma skin cancer or aerodigestive cancer
- No active systemic viral, bacterial, or fungal infections requiring treatment
- No serious concurrent illness that would preclude study compliance and follow-up
- No psychological, familial, sociological, geographical, or other condition that would preclude study compliance and follow-up

Expected Enrollment

51

A total of 18-51 patients (18 for phase I and 33 for phase II) will be accrued for this study.

Outcomes

Primary Outcome(s)

Safety at weeks 2-4 and then for 6 months
Maximum tolerated dose of Ad5CMV-p53 gene administered as an oral rinse at weeks 2-4 and then for 6 months
Transduction and efficiency of treatment as measured by Simon's optimal 2-stage design at weeks 2-4 and then for 6 months

Secondary Outcome(s)

Effect of p53 gene transfer on molecular biomarkers of p53 activity reduction as measured by immunohistochemical staining at baseline and during courses 1 and 6

Outline

This is an open-label, dose-escalation study of Ad5CMV-p53 gene administered as an oral rinse.

- ***Phase I:*** Patients receive Ad5CMV-p53 gene by intramucosal injection into the area of the lesion followed at least 2 hours later by Ad5CMV-p53 gene as an oral rinse on day 1. Patients then receive Ad5CMV-p53 gene as an oral rinse twice daily on days 2-5. Treatment repeats every 28 days for 6 courses in the absence of disease progression or unacceptable toxicity.

  Cohorts of 3-6 patients receive escalating doses of Ad5CMV-p53 gene as an oral rinse until the maximum tolerated dose (MTD) is determined. The MTD is defined as the dose preceding that at which 2 of 3 or 2 of 6 patients experience dose-limiting toxicity.

- ***Phase II:*** Patients receive treatment with intramucosal Ad5CMV-p53 gene as in phase I and Ad5CMV-p53 gene as an oral rinse at the MTD.

Patients are followed every 3 months for 1 year, every 6 months for 1 year, and then annually for 3 years. Patients then receive long-term follow-up annually for an additional 10 years.

Trial Contact Information

Trial Lead Organizations

M. D. Anderson Cancer Center at University of Texas

Gary L. Clayman, MD, DDS, Protocol chair	Ph: 713-792-6525; 800-392-1611 Email: gclayman@mdanderson.org
Scott Lippman, MD, FACP, Protocol co-chair	Ph: 713-745-5439; 800-392-1611

Registry Information

Official Title	Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity and Oral Pharynx via an Adenoviral Vector [NCI Supplied Agent Ad-p53, (INGN 201) (Advexin®) NSC 683550, IND# 7135]
Trial Start Date	2006-06-25
Registered in ClinicalTrials.gov	NCT00064103 [1]
Date Submitted to PDQ	2003-05-20
Information Last Verified	2007-01-25
NCI Grant/Contract Number	CA97007, CA16672

Note: The purpose of most clinical trials listed in this database is to test new cancer treatments, or new methods of diagnosing, screening, or preventing cancer. Because all potentially harmful side effects are not known before a trial is conducted, dose and schedule modifications may be required for participants if they develop side effects from the treatment or test. The therapy or test described in this clinical trial is intended for use by clinical oncologists in carefully structured settings, and may not prove to be more effective than standard treatment. A responsible investigator associated with this clinical trial should be consulted before using this protocol.

Table of Links

1 http://clinicaltrials.gov/ct/show/NCT00064103